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SHOCK, EXHAUSTION, AND RESTORATION IN WAR

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and DANIEL P. QUIRING, Ph.D.

The word shock is not scientific. It expresses neither the state of the patient nor the cause of his condition. The term is ordinarily used to denote a state of physical exhaustion which has been rapidly developed by traumatic, toxic, or thermal stimuli. But if a soldier with a crushed toe limps in an imperative retreat for several days in pain and distress, without food, drink, or sleep, and is finally found prostrated, is he in shock or exhaustion, or both? Can the most complete microscopic and clinical study determine the cause of his death? Even when there is a paramount cause, it can hardly be dissociated from other factors. There is probably no ultimate difference between the bloodless, intangible causes of exhaustion and the bloody, tangible causes of shock. These states have interchangeable values; they depend on some common biologic principle. When the mechanism of fatigue and exhaustion is understood, the mechanism of shock will be understood.

Shock presents a special problem in war, since soldiers are commonly subjected to factors causing depression and exhaustion. Contributing factors are intensely exciting emotions such as fear; extreme physical exertion as in forced marches; loss of sleep; hunger and thirst; excessive heat or cold; and physical injury involving great pain and loss of blood.

Although the state of shock is difficult to define, some of the forces that control shock—the forces that control life and death—can be measured and expressed in physical terms. A physical phenomenon constantly associated with living processes is the potential gradient between various parts of the living organism, notably between the brain and the heart, or between the brain and the liver.

The potential gradient between the brain and the liver, the brain and the blood in the left ventricle, or indeed the brain and any other organ or tissue of the body, can be accurately and continuously measured in experimental animals and expressed in millivolts.[1] Hence the normal power of an animal can be expressed in millivolts, and likewise the degree of excitation, depression, or exhaustion from any one, or

any combination of factors which may affect a soldier in war. The potential gradient may also be considered an index of the factor of safety of the animal at a given moment—that is, an index of the amount of energy that can be drawn upon until death occurs.

In experiments on 503 animals, with and without the use of anesthesia, we tested the effects of gunshot wounds, hemorrhage, and other physical injuries on various organs and tissues. We also used various depressing and stimulating drugs. In all these experiments death was found to coincide with the fall of the potential gradient to zero.

But a sharp distinction must be made between the two types of factor causing definite change in the potential gradient. A decrease in value is associated with (1) mechanical interference with the normal functioning of the organs of the experimental animal, or (2) a gradual decrease in the normal organic functions. An example of the first type is sudden momentary stoppage of the heart by interference with the superior laryngeal nerve or by direct injury of the heart; in such a case the gradient falls abruptly. A factor of the second type is continuous, prolonged trauma, hemorrhage, infection, loss of sleep, or intense emotion, causing an equally deep but gradual depression of the potential gradient. Any one or any combination of these factors may reduce the vital potential gradient to zero.

There is an important histologic difference between the effects of sudden and of prolonged depression of the body. This difference was observed in the cells of three organs: the brain, the liver, and the adrenal cortex. After sudden inhibition of circulation, respiration, or activity of the brain or medullary centers, postmortem microscopic examination showed no change in the cells of the brain, the liver, and the adrenal cortex. But after gradual exhaustion, over hours or days, by such factors as hemorrhage, pain, or loss of sleep, there were striking cellular changes in the brain, the liver, and the adrenal cortex.

Extensive study of these cellular changes has been reported.[2] The investigation included both wild and laboratory animals, as well as soldiers who had died from the stress and injuries of battle. In research extending over 9 years no physical changes were found in any muscle cell, voluntary or involuntary, though the muscular system constitutes the greater part of the body and takes the largest share in physical effort. Nor were there cellular changes in other ductless glands, abdominal viscera, lungs, fat, connective tissue, red blood cells, or bones. They occurred only in the brain, the liver, and the adrenal cortex.

Another series of experiments was undertaken to measure changes

in the electric conductivity, electric capacity, potential gradients, and temperature of the brain, the liver, and the adrenal cortex under many types of stimulation and depression.[3] The changes in the electric conductivity, electric capacity, potential gradients, and temperature of the brain, the liver, and the adrenal cortex paralleled the histologic findings as well as the degree of excitation, depression, and exhaustion of the subject.

It appears that the potential gradient between the brain and other parts of the body plays a vital role in the life and death of an animal. In our experiments the brain had positive polarity as compared with the liver and other organs of the body. This may mean that in the brain large numbers of positive ions are formed, which travel from the positive pole to the negative pole. However, the negative polarity of the body must be further explained.

There is a cell bearing the shape of a biconcave disk which possesses no nucleus in man and most other mammals, and exhibits very little metabolism. This cell, through its tumbling and the movement of the blood stream, is subjected to constant friction in the body. It is covered by a lipoid film approximately 1/2,500,000 cm. in thickness.[4] This cell is the red blood cell. It is ideally evolved to accumulate static electricity. The negative static potential depends on the speed of the blood flow, which in turn is regulated by the force and frequency of the heart beat.

There is a certain analogy to the bipolar plan of the living body in a copper-zinc electrolytic battery. Here most of the chemical energy of the battery is gained at the negative pole, while the positive pole produces positive ions through oxidation. The positive and negative ions in the battery balance each other. As the positive ions travel to the negative plate, causing the negative plate to perform chemical work, so the positive ions of the brain and the rest of the central nervous system travel to the negatively charged organs and tissues, causing them to perform their work.

When current is drawn from a Volta liquid battery, polarization occurs. If the flow of current is stopped, the battery recovers as depolarization takes place. A similar phenomenon takes place in tissue cells. If current is drawn from the cells, polarization occurs which manifests itself in fatigue, exhaustion, and eventually death. If the final state is not reached, and if the tissue cells are permitted to recover with sufficient rest, depolarization occurs and the body recovers.

With the complete, irreversible polarization of death, when the potential gradient is at zero, the changes that occur in the cells of the

brain, the liver, and the adrenal cortex are at their maximum. But when depolarization occurs, as after a period of sleep, the overwhelming microscopic changes in the cells disappear as if by magic. Equally, when the energy of the animal is again restored, do the electric conductivity, electric capacity, and potential gradients return to normal.

During one series of experiments 84 rabbits were kept awake continuously[5]. Though they were given food, drink, and comfortable surroundings, death from loss of sleep occurred on the average in 92 hours. If in addition to being kept awake rabbits were subjected to fear, injury, or intense conscious activity involving the energy systems—to intense stimulation of the brain, the liver, the adrenal cortex, and the heart—then exhaustion and death occurred within a few hours. The physical changes noted in the brain, the liver, and the adrenal cortex were identical with those produced by mere loss of sleep. That is to say, abnormal excitation, injury, and stimulation produced polarization of identical type but in a shorter period than uninterrupted maintenance of a conscious state.

As already explained, the brain possesses positive polarity as compared with the negative polarity of the liver, the blood, and the rest of the body. We believe that this conception explains the nature of shock and therefore the rationale of its prevention and treatment. When the brain is protected by nerve block, by gentle operation, by light anesthesia, by maintenance of normal temperature, the positive pole of the bipolar mechanism remains normal. On the other hand, when hemorrhage is immediately repaired by transfusion of whole blood or blood plasma, when the force and frequency of the heart beat are kept within normal range, then the negative pole is kept within the normal state. If both the positive and the negative potential are maintained, then there is a normal potential gradient. That is to say, life continues normally; shock is avoided.

In accordance with these principles has been developed the shockless operation and the modern treatment of shock in war and civil life. The following measures are most effective in the problems of surgery, whether in war or peace.

Pain should be relieved by adjusting painful dressings, splints, or tourniquets and arranging for maximum comfort. If pain cannot be relieved by other means, morphine should be given unless there are intracranial injuries or cyanosis is present. The body should be tilted with the head down.

The fluid balance should be established. In serious cases whole

blood or plasma transfusions should be given. Lost body heat should be restored by blankets, hot air, or hot water.

In the effort to restore the depressed energy, measures that lead to further exhaustion and shock are sometimes employed. Any drug that can act as a stimulant can further deplete the bodily energy. The overactivated soldier needs the opposite of stimulation, namely negativity. Interference with physiologic rest is interference with repair; therefore, no stimulants are to be used.

Local, regional, or spinal anesthesia, alone or supplemented by light inhalation anesthesia, is preferable to use of the heavy anesthetics, such as ether or chloroform. If the heavy anesthetics are necessary, anesthesia should be as light and short as is consistent with good surgery. Operations must be done deftly, quickly, and with a light touch.

The restorative power of warmth, food, drink, comfort, and rest cannot be overemphasized; but the most potent reparative agent in exhaustion and shock is deep, untroubled sleep. Comfort, quiet, and assurance are beneficial in large part because they lead to the deep polarization of sleep. This is attested in the intense phases of war. Soldiers sleep in trenches, in mud, on stones, in rain, under bombardment. They sleep in shell holes, on the march, and on horseback. They sleep with compound fractures or abdominal perforations; they sleep despite pain and hunger and thirst; sleep though captured; sleep on stretchers awaiting operations. When at last in a comfortable bed, an exhausted soldier may sleep heavily for two days. Once the desire for sleep has been satisfied, the soldier has wants, appreciates pain, experiences hunger and thirst. The shrunken face fills out, exhaustion is relieved, normal life is restored.

SUMMARY

Although the modern treatment of shock is increasingly effective, the mechanism of shock is not thoroughly understood, and the word itself is loosely and unscientifically employed. Shock may be defined as an extreme stage of exhaustion—as the severe diminution or derangement of the forces that maintain life.

The understanding of shock may be clarified by the conception of the body as a bipolar mechanism. According to this view, the brain is electrically positive as compared with the rest of the body. The blood, the liver, the heart, and all other organs and tissues have negative polarity with reference to the brain and the rest of the nervous system. This may be explained by oxidation in the brain, which produces posi-

tive ions, and by charge-up of the red blood cells in the heart with static negative electricity.

A potential gradient exists between the brain and the rest of the body. This has been demonstrated in experiments on 503 animals. It was found that under various stimulating, depressing, and exhausting factors, the potential gradient varied directly with the degree of excitation or depression of the animal, falling to zero at death. The drop in the gradient occurred either abruptly or slowly.

In a series of tissue studies it was noted that the same exciting or depressing factors which caused a rise or fall in the potential gradient also caused destructive changes in the cells of the brain, the liver, and the adrenal cortex, but in the cells of no other organs or tissues of the body. These cellular changes were not seen when death was caused by sudden depression, but only after prolonged depression of the organism.

Electric conductivity, capacity, potential gradients, and temperature of the brain, the liver, and the adrenal cortex of animals under stimulation and depression also paralleled the excitation and depression of the organism as a whole, and corresponded with the histologic findings.

It is therefore suggested that the potential gradient, measured in millivolts, between the brain and other organs and tissues accurately indicates the degree of shock in the animal body.

It is also concluded that in the depression or failure of organs essential to life, a phenomenon takes place in the body that resembles polarization in a Volta liquid battery. If before death occurs the tissue cells are permitted to rest, depolarization (sleep) takes place, and the body recovers. These conceptions are in harmony with modern methods of prevention and treatment of shock.

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CHEMICAL PNEUMONIA IN WORKERS EXTRACTING BERYLLIUM OXIDE

Report of Three Cases

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and MORRIS G. CARMODY, M.D., F. A. C. S.*

In the past 22 months 3 men employed in the extraction of beryllium oxide from the raw ore have been seen at the Cleveland Clinic. They presented symptoms of a chemical pneumonia which we believed to be attributable to their occupation. In each patient the syndrome was characteristic and identical, and in each recovery was complete. One man returned to the same occupation, developed a recurrence of his initial pneumonia, and is again making a satisfactory recovery.

We believe that the chemical pneumonia is due to the inhalation of irritants in the process of the extraction of beryllium oxide. The specific etiologic agent is unknown. It may not be beryllium per se but chemical compounds formed outside or inside the respiratory tract during the processing of the ore.

Beryllium belongs to the same chemical group as magnesium and calcium. It is usually found as beryl, a double silicate of beryllium and aluminum. It is used as an alloy to harden and strengthen other metals; it prevents corrosion, augments the electric conductivity of copper, and is easily permeable to x-rays as is shown in figure 1.

In the American literature we have been unable to find a reference to the toxicity of beryllium or its compounds. In the foreign literature Caccuri[1] reported experimentally produced hepatic and renal changes in beryllium poisoning. He studied the effects of beryllium carbonate, nitrate, and oxide on the liver and kidney in rabbits and found that the nitrate causes the greatest damage. Volter[2] reported the experimental toxicity of beryllium fluoride and chloride and found the former to be more toxic. These compounds were found to precipitate proteins in vitro, inhibit the life process of infusoria, and denature cell protoplasm. Volter reported that beryllium fluoride can paralyze the central nervous system in the higher forms of life with death resulting from paralysis of the respiratory center.

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An article in Occupation and Health[3] describes one method used in the preparation of beryllium. This method involves four processes.

1. Beryl and sodium fluorosilicate are pulverized together liberating large amounts of dust.

2. The mixture is fused in kilns. Some gases are given off, e.g., SiF_4.

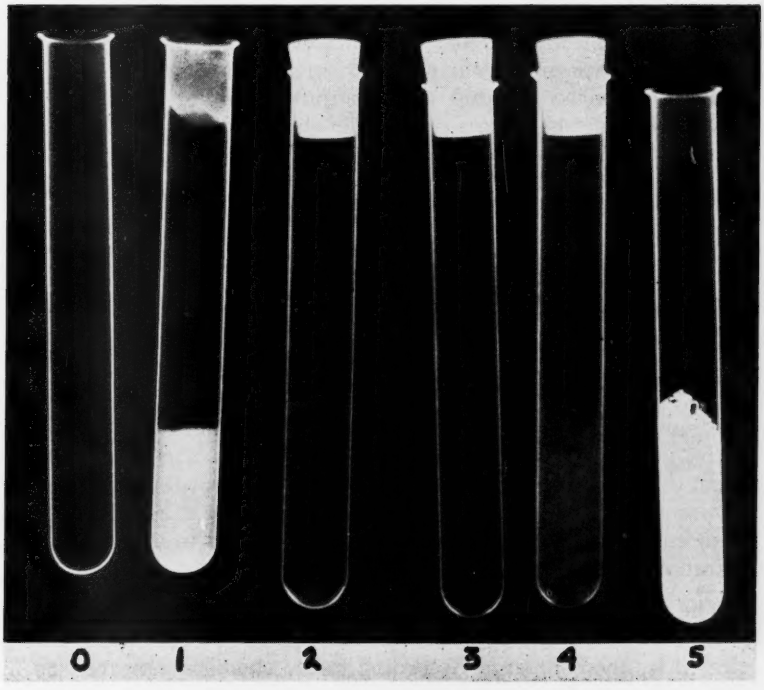

FIGURE 1. This figure illustrates the relative radiotranslucency and radio-opacity of (0) air; (1) $BaSO_4$ %10; (2) $BeSO_4$ %10; (3) BeO crystals; (4) $BeSO_4$ crystals; (5) $BaSO_4$ crystals. It is evident that BeO crystals (3) are essentially radiotranslucent.

3. The resulting mass is again pulverized and treated with hydrofluoric acid to dissolve out beryllium as beryllium oxyfluoride. Dust of silicates, fumes of the oxyfluoride, and vapors of hydrofluoric acid may be evolved during this stage.

4. Beryllium oxyfluoride is heated in a crucible or treated elec-

trolytically to recover pure beryllium. Gases and smokes given off resemble those mentioned in the third stage.

This article states that the precise nature of the beryllium compounds given off in smoke and dust is not known. The presence of hydrofluoric acid and silicon fluoride in the air must be kept in mind. Other fluorides also may be present.

The foregoing report mentions the pathology occurring in the skin and mucous membranes. Particular attention is called to "a metal fume fever," i.e., paroxysmal cough with a small amount of expectoration, increased dyspnea, cyanosis, and slight fever usually with complete recovery. During the disease process the clinical findings were cyanosis, dyspnea, reduction of chest expansion, and numerous moist râles without definite localization. The syndrome continued for 3 or 4 weeks with alternating remissions and exacerbations. X-rays of the chest had a "reticulated" appearance with small nodules resembling those seen in miliary tuberculosis. The condition was described as a bronchiolalveolitis or peribronchiolalveolitis.

Gelman[4] in Moscow reported a number of cases with this clinical picture. He believed that the disease in their beryllium "foundry" was due to the action of fluorine which he thought was separated from beryllium oxyfluoride at the level of the bronchioles and alveoli. It was his impression that it takes time for enough fluorine to accumulate to cause symptoms, and that it continues to separate as long as any beryllium oxyfluroide is present which accounts for the prolongation of symptoms. The fumes are said to be able to travel in air in toxic concentrations for 100 yards or more.

The chemical procedure or formula used for the preparation of beryllium oxide at the plant at which our patients worked has not been released by the company. According to the chemists, however, no fluorides are used. Despite this difference in preparation of beryllium the symptoms and physical findings of our patients closely resembled those that have been reported to occur when fluorides were used in the preparation of beryllium.

The symptoms of the three patients reported here were identical. Each man began to note the insidious onset of his disease by a gradual decrease in his vital capacity. Soon thereafter a dry cough was noted which was never very productive. In all instances the expectoration of mucoid or frothy sputum was slight and occasionally blood tinged. The most disturbing symptom was the progressive dyspnea with the

ensuing severe apprehension. In each patient the disease ran a low grade febrile course in which the temperature never rose above 100 F.

The physical findings were also identical: low grade fever, shallow rapid respirations, mild to moderate cyanosis with fine crepitant râles throughout the lower half of both lungs.

Two of the patients had bronchoscopic examinations: one revealed a hyperemic tracheobronchial mucosa; and the other showed additional evidence of chronic irritation with the presence of a patchy exudate throughout the visualized tracheobronchial tree. The aspirated secretions and expectorated specimens, or both, were negative for all pathogens in all cases. There was no deviation from the normal in the white blood count or in other laboratory tests.

The onset of symptoms preceded the roentgen changes by at least 3 weeks. The appearance of the chest films then varied with the stage and severity of the disease. The x-ray findings in order of progress were: (1) diffuse haziness of both lungs; (2) subsequent development of soft irregular areas of infiltration with prominence of the peribronchial markings; (3) absorption of soft exudative infiltration and the appearance of discrete small nodules scattered throughout both lungs; (4) clearing of lung fields.

The roentgen changes were bilateral and diffuse in all cases and followed the same general pattern. The exudative and nodular infiltration regressed within one to 2 months after which the chest appeared entirely normal. Identical roentgen changes were found by one of us (R.H.) on reviewing the chest films of 6 additional patients. These patients were from the same beryllium plant and had symptoms similar to those in the 3 cases reported in this paper.

The term tentatively used in the diagnosis is chemical pneumonia, although a more accurate one might be chemical pneumonitis or chemical bronchiolitis. As mentioned previously, the condition has been described in the foreign literature as a bronchiolalveolitis or paribronchiolalveolitis.

The average loss of time from work in the 3 cases was 3¾ months.

CASE REPORTS

Case 1. A man 28 years of age came to the Clinic on February 11, 1941 complaining of shortness of breath with a slightly productive cough of one month's duration. He stated that the expectoration had been slightly blood streaked on several occasions. He had lost 11 pounds in weight.

There was a moderate elevation of temperature, 99.6 F., and abnormal physical findings in the chest. There were decreased respiratory excursions with a respiratory rate of 30, and numerous scattered fine crepitant râles were heard throughout both lungs. The mucous membranes were slightly cyanotic.

X-ray examination of the chest showed a diffuse haziness of both lungs, prominence of the peribronchial markings, and irregular areas of soft nodular infiltration.

Bronchoscopy revealed patchy areas of whitish adherent exudate on the visualized tracheobronchial mucous membrane. There were no ulcerations, tumefactions, nor changes in the size of the lumen of the bronchial tree. There was a minimal amount of secretion which upon aspiration was found to be negative in all respects on smear and culture.

Expectorated mucoid specimens were negative for all pathogens; the blood counts were normal; and all the other routine laboratory studies revealed normal values.

On a program of rest the patient's symptoms entirely subsided in 3 weeks, and an x-ray examination of the chest on March 11, 1941 showed a complete return to normal.

The roentgen films in this case have not been released by the State Industrial Commission.

Case 2. A man 55 years of age was seen on May 3, 1942 with symptoms of shortness of breath and a slightly productive cough of 5 weeks' duration. As in the preceding case the positive physical findings were a low grade fever, the temperature being 99.8 F., mild cyanosis, shallow rapid respiration, and fine crepitant râles scattered throughout the lungs being most pronounced in the lower two-thirds.

Stereoroentgenograms showed essentially the same findings as in the previous case.

A bronchoscopic examination showed a mild generalized hyperemia of the tracheobronchial mucosa without other pathology. A minimal amount of rather frothy secretion was aspirated and was negative on smear and culture.

Expectorated mucoid secretions were negative bacteriologically. The blood counts and all other laboratory tests were normal.

This patient was advised to rest for 3 months and then return for a recheck examination. When seen again on August 26, 1942 he stated that he had been completely symptom free for over one month. A progress x-ray examination of his chest was found to be entirely normal. The patient was advised to return to some simple form of work other than at the plant in which he had contracted the chemical pneumonia. On November 12 this patient returned and related that he had experienced a recurrence of his previous symptoms in the past 3 weeks. Contrary to our advice he had returned to work at the beryllium plant on September 16. The physical findings were identical to those of his initial examination, and x-ray examination of his chest showed a recurrence of the chemical pneumonia. He was hospitalized in his own town, and after a rather stormy course he is now convalescing satisfactorily.

This case illustrates the recurrence of identical symptoms in a patient following reexposure in his occupation. As in the first case the roentgen films have not been released by the State Industrial Commission.

Case 3. A boy aged 17 entered our hospital on August 27, 1942 with the symptoms of marked dyspnea and a slightly productive cough with occasionally blood-tinged expectoration of 3 weeks' duration. The patient informed us that he had been

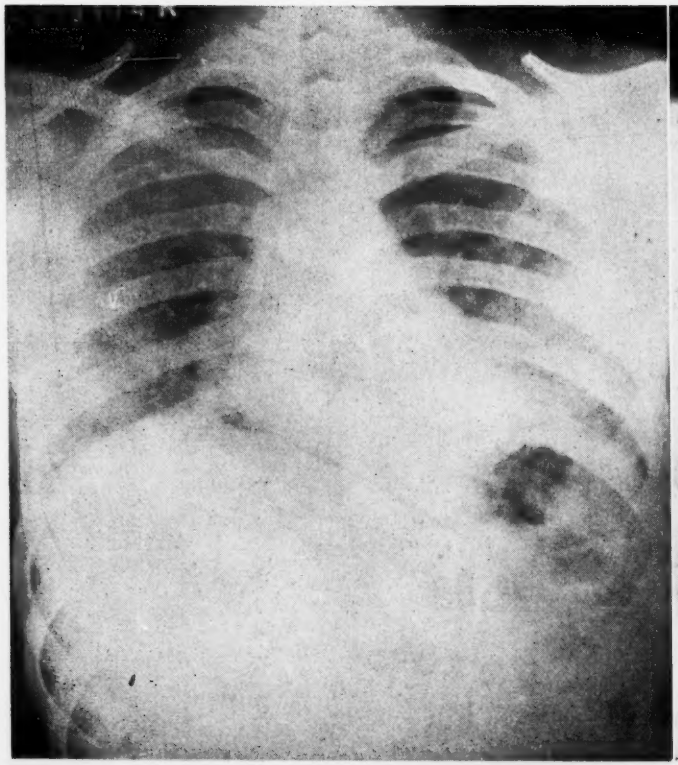

FIGURE 2. This chest represents the changes at the height of the disease. The roentgen film shows a diffuse soft patchy infiltration in both lungs with prominence of the peribronchial markings and a little elevation of both diaphragms.

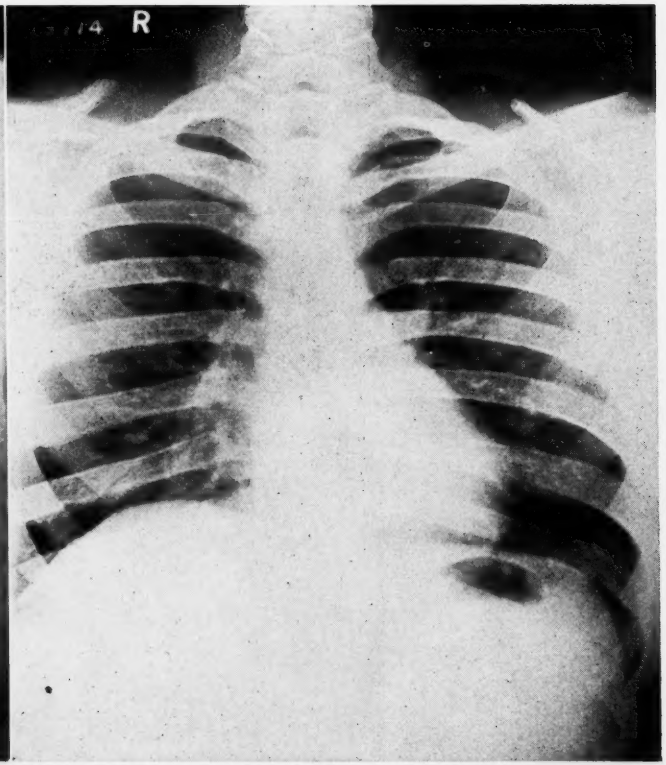

FIGURE 3. This chest film was made 6 weeks after the film in figure 2. At this time both lungs appear entirely normal.

employed at the chemical plant for 3 months and was classified as a general helper, "doing everything around the plant."

The initial examination revealed considerable cyanosis, a temperature of 99.8 F., and extreme dyspnea. Bronchovesicular breath sounds were present over the lower two-thirds of the chest both anteriorly and posteriorly with a roughening and prolongation of the expiratory phase as compared with the inspiratory; the total excretory excursion was very shallow with a rate of 48.

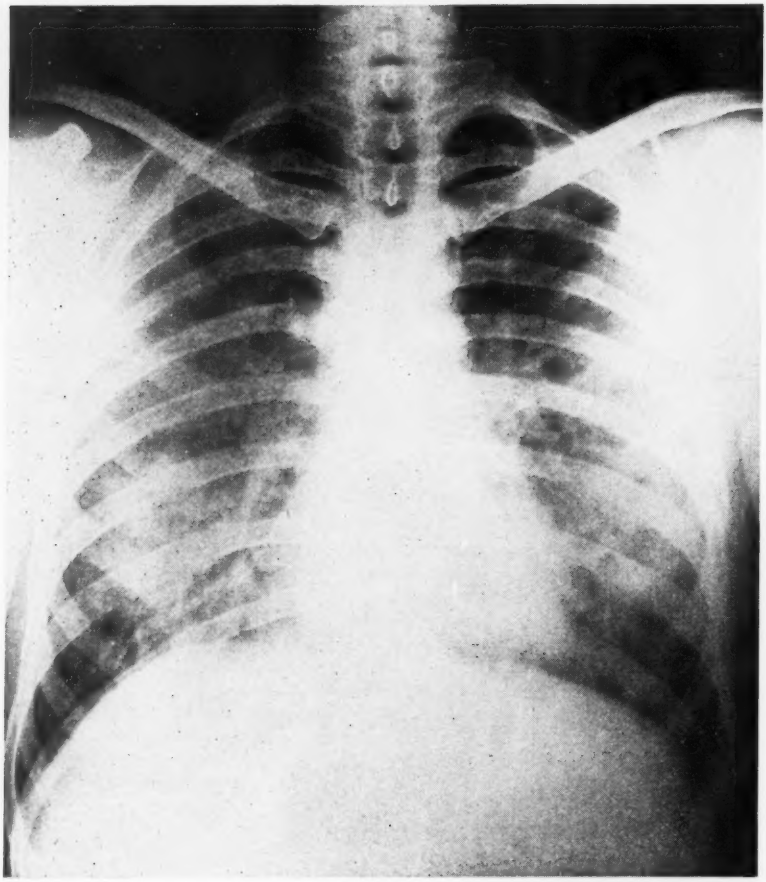

Figure 4. This chest film illustrates a chemical pneumonia which developed in a patient working in a rayon factory. There is a diffuse bilateral soft infiltration present. This appears in irregular conglomerate patches and resembles the changes occurring in the 3 patients working in the beryllium plant.

Stereoroentgenograms of the chest again demonstrated the diffuse haziness, soft patchy infiltration, and the prominence of the peribronchial markings. (Fig. 2) In this case there was also some elevation of both diaphragms.

The patient was hospitalized for 22 days and was confined within an oxygen tent for the greater part of the first 12 days. His temperature ranged between 99.4 F. and 100 F., but returned to normal the last 5 days of his stay. Roentgenograms made at 5 to 7 day intervals initially showed a progression of the pulmonary pathology and then a gradual recession. Later films assumed more of a mottled, nodular character in contrast to the initial diffuse haziness.

The patient was discharged to his home on a continued rest regimen. Six weeks later he reported that he had been completely symptom free for the previous 2 weeks. The last x-ray examination made on this patient reveals a complete return to normal as is shown in figure 3.

This patient suffered a more severe disability than the other 2 patients. It is interesting to note that as a general helper he never spent any appreciable time at any one phase of the extraction of beryllium oxide. We had the opportunity to review chest films made at 1 to 2 week intervals after the onset of his symptoms. No change was evident for the first month after which x-rays showed a characteristic progression of the disease and finally clearing of the lungs.

Symptoms and roentgen changes identical to those described in the 3 foregoing cases were found in a 28 year old man who was employed in "the mixing room" of a rayon factory. He informed us that he had worked there for over 5 years, and that 8 other men in the same department had recently become ill and apparently were convalescing satisfactorily away from work. Our diagnosis in this case was chemical pneumonia of undetermined etiology. (Fig. 4)

This case has been mentioned as a chemical pneumonia with symptomatology and roentgen findings identical to those of the 3 cases reported in the beryllium industry, although apparently without exposure to a beryllium compound. This would suggest that beryllium itself is not the etiologic factor.

In our own research department and in the plant manufacturing beryllium oxide, studies are being carried out with the hope of determining the exact etiologic agent for the chemical pneumonia as illustrated in these 3 patients. Experimental animals have been placed in various places in the plant to study the effects of exposure. We hope to be able to add further information in a subsequent report.

SUMMARY

Three cases of chemical pneumonia occurring in a war industry manufacturing beryllium oxide are presented. The chemical formula or agents used in this process have not been made known by the manufacturer.

The 3 cases reported had identical symptoms and roentgen findings. The characteristic symptoms consisted of dyspnea, a relatively non-productive cough with occasionally blood-tinged expectoration, and a low grade fever. The roentgen changes in the chest which appeared about 3 weeks after the onset of symptoms revealed a diffuse haziness of both lungs, prominence of the peribronchial markings, soft irregular areas of infiltration, and discrete small nodules. These changes were dependent on the stage of the disease. The 3 patients recovered with a complete return of the lungs to normal on chest x-ray.

Additional studies are being made to determine the specific inhaled etiologic agent in this industrial disease attendant to the war effort. The loss of time from work in these 3 cases averaged 3¾ months.

We wish to acknowledge our appreciation to Dr. John M. McDonald, Director of the Bureau of Occupational Diseases, Baltimore City Health Department, Baltimore, Md. for his interest and cooperation in independently reviewing the foreign literature bearing on occupational diseases in the beryllium industry.

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RENAL RICKETS

Report of a Case

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Renal rickets is rickets resulting from chronic renal insufficiency. Renal dwarfism may refer to the same condition and implies dwarfism caused by renal rickets. Renal infantilism refers to such cases as show dwarfism plus hypoplasia of the genitalia. Both the term dwarfism and infantilism in this regard have the disadvantage of distracting from the idea that kidney disease and rickets are the underlying disorders. In some instances renal infantilism is an actual misnomer applying to infantilism with diabetes insipidus without concomitant kidney disease, both the infantilism and the diabetes being pituitary in origin.

In some cases renal rickets may be difficult to distinguish from primary hyperparathyroidism especially when it occurs in growing individuals. In some of the cases in the literature reviewers have disagreed on the origin of the disease, the same cases being classified by one author as primary renal disease and by others as primary hyperparathyroidism. The reason for this is that in both instances when the kidney damage reaches a certain point the effect upon blood chemistry, calcium balance, and the skeleton may become indistinguishable.

In cases in which the differential diagnosis is difficult, the history is one of the most important points. In hyperparathyroidism skeletal changes precede evidence of renal damage, while in renal rickets kidney disease has existed for a long time before bony damage becomes apparent. Hyperparathyroidism may exist without any recognizable x-ray evidence of bony disease, but in those instances in which the parathyroid disease has resulted in severe kidney damage clear-cut changes in the bone might be expected. It is well to remember also that renal rickets usually results from a congenital deformity of the lower urinary tract, so that the finding of such a condition may help greatly in the diagnosis. Both in rickets and in renal rickets parathyroid enlargement and parathyroid hyperfunction have been demonstrated. In primary hyperparathyroidism a single parathyroid adenoma is likely to be present, whereas in secondary hyperparathyroidism due to kidney disease hypertrophy of all the parathyroids occurs. Albright[1] describes a third type of hyperparathyroidism in which all parathyroids are hyperplastic and

in which the hyperparathyroidism appears to be primary in type. It is assumed to be primary because there is no other condition evident to suggest that it is a compensatory mechanism. Doubt has been expressed by some as to whether such a condition is primary or not. One point which favors the primary nature of the condition is that excision of some of the glands leads to clinical improvement. The validity of such an argument remains to be proved.

CASE REPORT

A 15 year old boy was seen in September, 1938 with a complaint of "knock-knees" of 7 months' duration.

At the age of 2 years he had been admitted to another hospital because of vomiting, fever, abdominal distention, and "difficulty in urination." A diagnosis of acute ileus had been made, and the patient had improved on conservative therapy. Nothing is known of the urinary symptoms at that time, except for the fact that there was "difficulty in urination." Apparently he got along fairly well subsequently.

At the age of 6 he had been readmitted to the same hospital for circumcision because of a redundant prepuce.

At the age of 7 he had been admitted for the third time to the same hospital with a history of fever, malaise, and weight loss of 3 weeks' duration. He also complained of pain in the left side of the abdomen. At that time his father stated that there had been a mass in the lower abdomen since the child was 2 years of age. An x-ray showed an enlarged bladder with an irregular filling defect in the posterior portion. An operation was performed on November 4, 1930, and the wall of the bladder was found to be hypertrophied. Bougies introduced through the urethra met resistance at the entrance of the bladder and, when enough force was exerted, entered the bladder "almost curving like a hairpin and proceding up towards the symphysis." A diagnosis of a congenital flap valve at the urethral opening was made, and this "valve" was cut. A suprapubic catheter was inserted, and the incision was closed. The patient was discharged on January 29, 1931, at which time he was voiding normally. He had gained 20 pounds in weight during his hospital stay. The suprapubic wound drained urine for about one year, but the patient had no urinary symptoms except for occasional nocturia. However, his mother stated that she believed that pus had been present in the urine most of the time since the operation.

The patient had grown normally until the age of 6 years; after which he grew relatively little. There was marked anorexia. No urinary symptoms were present except for occasional nocturia.

Physical examination revealed an undeveloped and undernourished boy. The temperature and pulse were normal, and the blood pressure was 126/84. His height was 56 inches, his weight was 75¾ pounds, and his age 15 years. The skin and mucous membranes were pale. The external genitalia were underdeveloped for his age, and there was no sign of puberty. There was a genu valgum deformity of both legs. (Fig. 1)

Repeated urinalyses revealed a specific gravity of 1.007 to 1.018 with a trace of albumin. Numerous white blood cells were found in all specimens. Cultures of ureteral urine obtained at cystoscopy showed Staphylococcus albus. The initial red blood cell count was 2,540,000, and the hemoglobin was 43 per cent. Temporary improvement

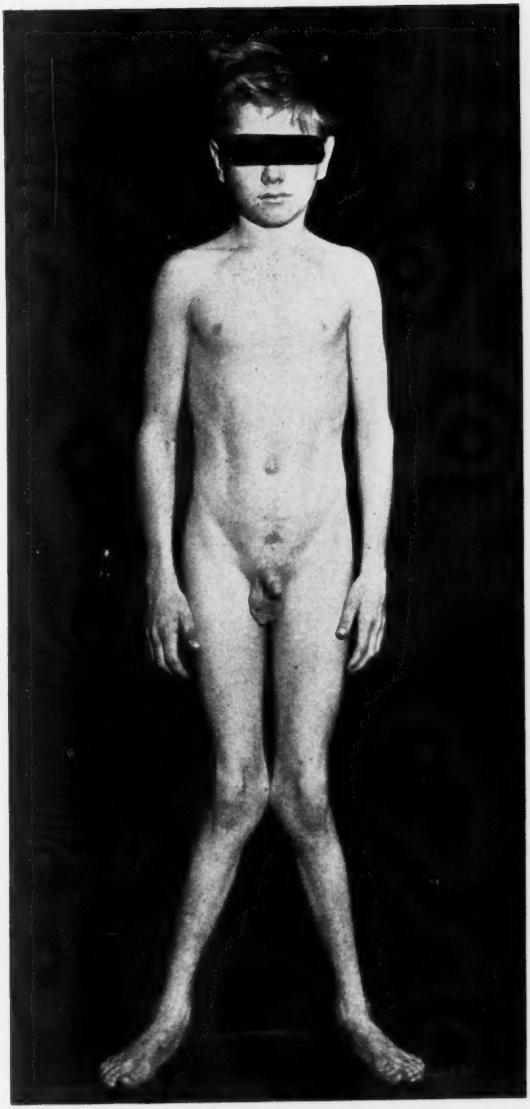
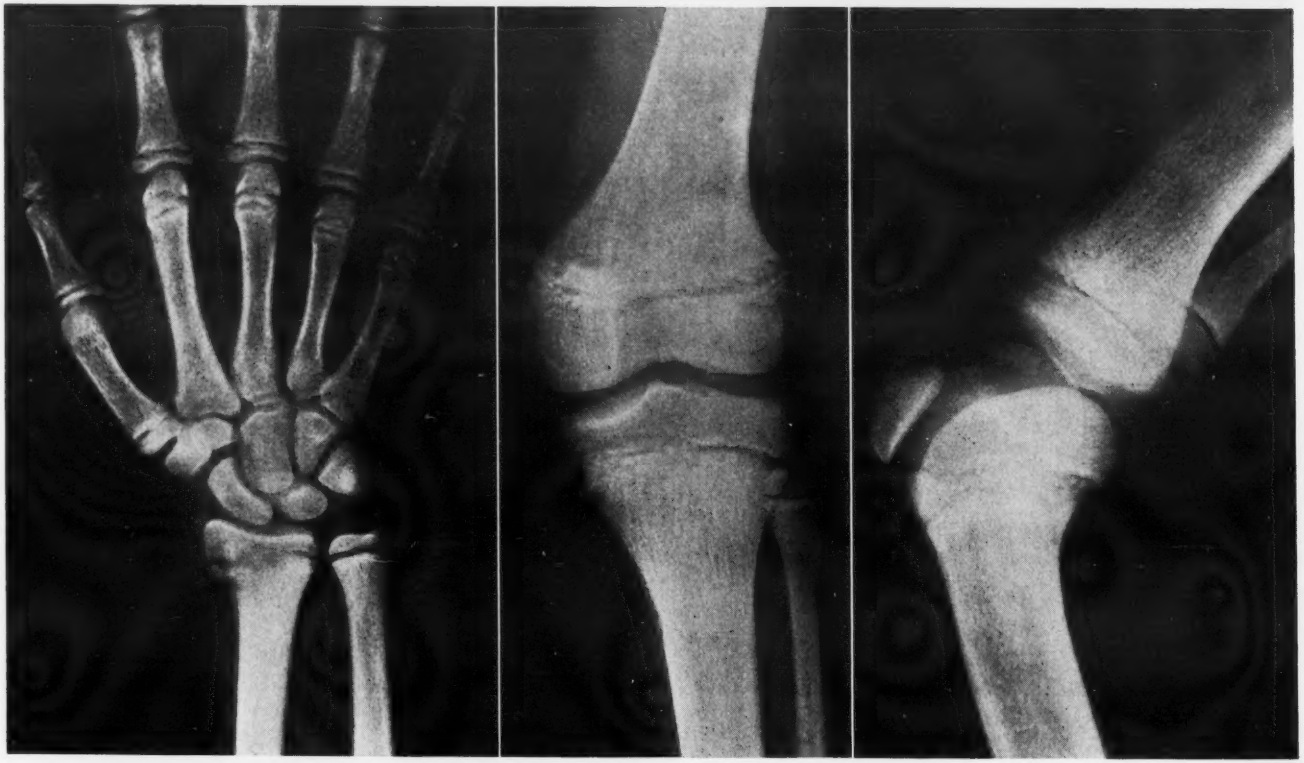


FIGURE 1. Showing extreme genu valgum.

FIGURE 2



A. Roentgenogram of the left wrist showing similar changes and, in addition, a slight displacement of the epiphysis.

B and C. Roentgenogram of the left knee showing irregular ossification at the metaphysis of both the femur and the tibia and narrowing of the epiphyseal line.

in the blood counts was appreciated after transfusion. The white blood cell counts were normal. The blood sugar was 104 mg. per 100 cc., the urea 150 to 219 mg., the uric acid 5.0 mg., the creatinine 4.2 to 4.6 mg., the cholesterol 145 mg., the calcium 9.5 mg. on two occasions, the phosphorus 5.5 to 6.8 mg., the serum alkaline phosphatase was 10.9 Bodansky units (normal 4 units), the blood chlorides 610 mg. per cent, and the blood carbon dioxide combining power varied from 19.5 to 42.4.

The urea clearance test showed 11 per cent excretion in the first hour and 6 per cent in the second hour.

Roentgenograms of the left knee showed irregular ossification at the epiphysis, and the epiphyseal line was narrowed and fuzzy in appearance. There was no broadening or cupping present, and the adjacent bones appeared to be normal. The left wrist showed similar changes in the distal end of the radius. In addition, there was a slight displacement of the epiphysis and a small amount of static subperiosteal calcification. The epiphyses of the metacarpals showed minimal changes. There appeared to be slightly irregular ossification at the epiphysis of both hips. The appearance of the bones seemed to be consistent with a diagnosis of renal rickets. (Fig. 2)

Cystoscopy was performed in the hospital, and about 50 cc. of residual urine was obtained. The bladder showed a moderate degree of trabeculation, but no evidence of inflammation. Ureteral catheters were passed without meeting obstruction. The cystoscope was withdrawn into the bladder neck, the appearance of which simulated bilateral hypertrophy of the prostate. The verumontanum appeared to be normal, and the prostatic urethra did not appear to be lengthened. Bilateral pyelograms revealed extreme hydronephrosis of each kidney with associated marked dilatation of each ureter. (Fig. 3)

A suprapubic cystostomy was performed on September 24, 1938. The patient was discharged from the hospital on October 12, 1938. He was instructed to follow a high calcium, low phosphorous diet and to take calcium lactate, ferrous sulfate, and vitamin preparations daily. He was seen three days later because the suprapubic tube had come out, and this was reinserted.

He was admitted to Lakeside Hospital, Cleveland,* on January 21, 1939, because of hematuria and hemoptysis of 3 weeks' duration. The physical examination was much the same as at the time he was seen by us. The suprapubic catheter was still in place. The urine was grossly bloody, and there was a marked anemia. The blood urea was 98.3 mg. per 100 cc., the creatinine 8.7 mg., the calcium 6.6 mg., the phosphorus 10.4 mg., the serum phosphatase was 13.3 mg., and the chlorides were 626 mg. The carbon dioxide combining power was 31.1 volumes per cent. The phenosulfonphthalein renal function test showed no excretion of the dye in 2 hours. The urea clearance test resulted in 2.7 per cent excretion in the first hour and 4.5 per cent in the second.

Cystoscopy showed a moderate generalized cystitis. The right ureter was catheterized, and marked hydronephrosis and hydroureter were found. The left ureter could not be catheterized. A median bar formation in the prostate was suspected. The patient was discharged on January 25, 1939, to be followed in the out-patient department. He did not return for observation, however, and was seen in the emergency ward on March 13, 1942. The suprapubic catheter had not drained for 2 days. During the previous 24 hours, the respirations had been deep and rapid, and he had experienced several chills. The patient's temperature was 38 C., the pulse was 128 per minute, the respirations 48 per minute, and the blood pressure 120/76. Small hemorrhages were

* We are grateful to Lakeside Hospital and especially to the Department of Pathology for allowing us to publish excerpts from their records, and to Dr. G. M. Jilovec for his studies of the tooth.

seen in both eyegrounds. Many moist crackling râles were heard over the base of the right lung. The urine showed a large amount of albumin and many white blood cells. The red blood cell count was 850,000 and the hemoglobin content was 14 per cent; the white blood cell count was 8,600. The blood urea nitrogen was 188 mg. per 100 cc., the creatinine 15.2 mg., and the carbon dioxide combining power was 23.3 volumes per cent. The patient became rapidly worse in spite of treatment and died the day following admission.

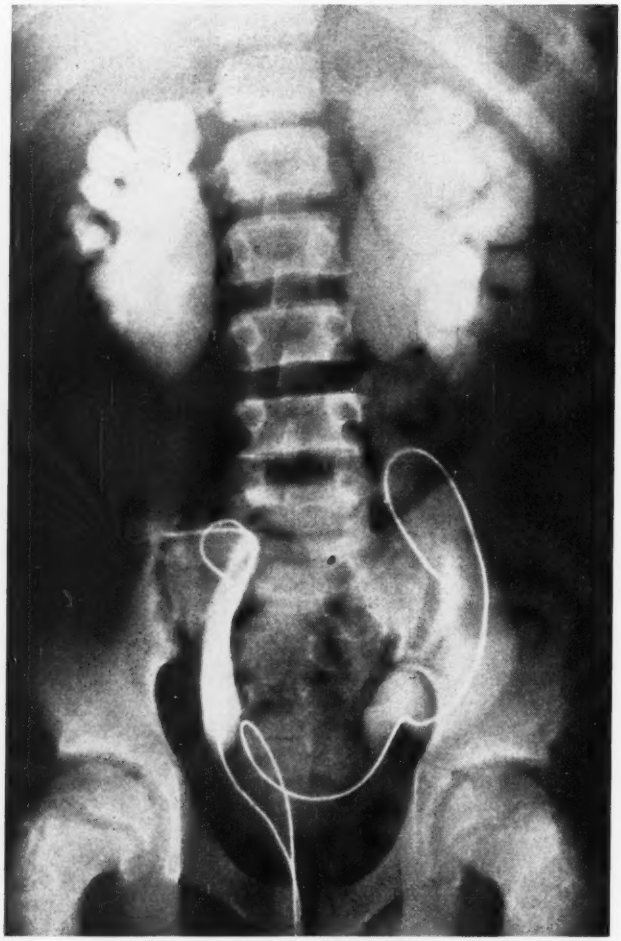


Figure 3

Retrograde pyelograms showing bilateral hydronephrosis and hydroureter.

Autopsy revealed the kidneys to be small, the right one weighing 75 grams and the left 90 grams. The capsule stripped with difficulty to reveal a rough, nodular surface. The kidney substance was cut with increased resistance. There was dilatation of the renal pelves and calyces, and in many portions the entire renal parenchyma was reduced to a mere shell only 1 mm. thick, although in other areas the thickness was as much as 1.5 cm. The usual architecture of the cortex and pyramids was absent, and the boundary between the cortex and the medulla could not be distinguished. The small renal vessels were thick walled and prominent. The renal pelves were extremely dilated, as were the ureters, which measured 2.5 cm. in circumference.

The bladder was thick walled, with a suprapubic fistulous communication with the exterior. The mucosa was thrown up in thick folds and was markedly hyperemic. The ureteral orifices were widely patent. A slight elevation of the urethra was present at the bladder neck, and in this region the urethral floor was irregular and slightly nodular. The prostate was quite small.

Microscopic examination of multiple sections of both kidneys showed marked destruction of the renal substance and distortion of the usual architecture. The glomeruli were greatly reduced in number, were rather cellular, and in certain instances were surrounded by a thick zone of fibrous tissue. There was widespread fibrosis throughout the kidney and some focal round cell infiltration. No normal tubular epithelium was seen. Most of the tubules were greatly dilated and lined with flattened or low cuboidal cells, containing a pink-staining, homogenous material. Other tubules were extremely small and surrounded by fibrous tissue. The arterioles showed a considerable degree of thickening of the wall, particularly of the intima, and some reduction in the size of the lumen. There was edema and round cell infiltration of the connective tissue beneath the epithelium of the renal pelvis.

Sections of the ureters showed a thick, edematous, fibromuscular wall. The mucosa was composed of a layer of transitional epithelium which was piled up in places in such a way as to suggest squamous metaplasia. Beneath this there was a marked infiltration of small round cells and plasma cells.

The bladder wall showed edema, fibrosis, and infiltration with small round cells and plasma cells. The mucosa was composed of transitional cell epithelium. Longitudinal sections through the bladder neck from the verumontanum to the trigone showed transitional cell epithelium beneath which there was edematous tissue infiltrated with small round cells. There was chronic inflammation in the portion of the prostate in this region. In other sections of the prostate there was moderately dense fibromuscular tissue containing glands of the usual type and small areas of round cell infiltration.

In the posterior capsule of the thyroid 5 small bodies were found. These bodies were orange and resembled enlarged parathyroid glands. The weights of these glands were 58 mg., 85 mg., 92 mg., 128 mg., and 185 mg., giving a total weight of 548 mg. The average total weight for these glands should be about 100 mg.

Microscopic examination of the parathyroid glands showed that almost all of the cells were chief cells. The chief cells had the usual appearance, containing large round chromatic nuclei and finely granulated cytoplasm. In a few portions there was formation of alveoli.

Sections were made through the distal epiphysis of the left radius and the proximal epiphysis of the right tibia. Microscopic examination of these sections showed prolifera-

tion of the provisional zone of ossification. (Fig. 4) Some of the bony trabeculae had outer rims of osteoid tissue. In one of the sections there was an infraction of the cartilage, which was replaced by a fibrinoid type of material. The bony tissue itself differed from that usually seen in vitamin D deficiency rickets in that it was poorer in calcium. A 6 year old molar was extracted, decalcified, and sectioned. Nothing could be demonstrated which is not commonly found in teeth in this area. Unfortunately, no teeth which were calcifying later in the life of the patient were examined.

The examination of the other organs showed no significant findings except for bronchopneumonia. The thyroid, adrenals, pancreas, and testes were normal.

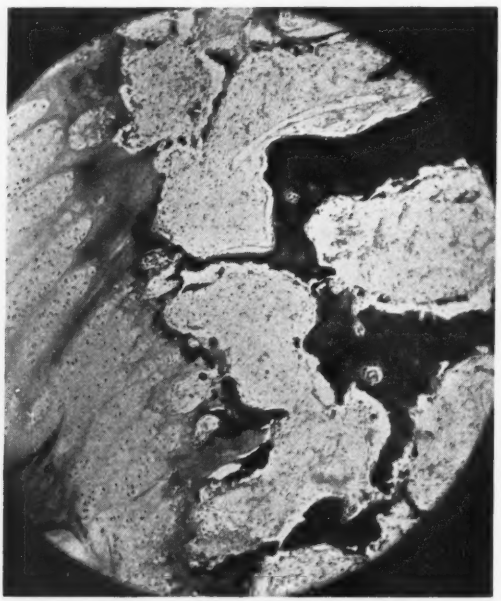


FIGURE 4. Section of the bone showing the irregular zone of advancing ossification and osteoparasis.

COMMENT

What causes such parathyroid enlargement? The answer must be theoretical. To begin with, renal failure results in many changes including phosphorus retention and chronic acidosis. The primary action of the parathyroid hormone appears to be upon the kidney, and its primary effect is in increasing the rate of phosphorus excretion. This is the first effect to be measured after injection of parathyroid extract. It seems reasonable to assume then that an abnormally high blood phosphorus

level may stimulate parathyroid activity and lead to overwork hypertrophy. A second factor is the tendency to low blood calcium.

What causes the blood calcium to be low? Several factors may be operating. The high phosphorus levels tend to bring the blood calcium down. The tendency to low calcium levels is further aggravated by the chronic acidosis which increases the excretion of calcium. It seems likely also that the excretion of phosphorus through the bowel would interfere with proper calcium absorption.

Why does the bone disease occur? This is not known, but here again it may be worthwhile to theorize. Phosphorus retention in itself obviously could not be an adequate explanation. There are several possible explanations. The first is that chronic acidosis leads to a continued high rate of calcium excretion, and this, we believe, is the chief factor. The very high level of calcium in the stool represents both unabsorbed calcium and excreted calcium. In this case the patient's nutrition was poor. He refused most of the food offered him, and no attention had been given to his receiving supplementary vitamins. It seems likely therefore that Vitamin D deficiency was an additional factor in producing calcium starvation.

What is the evidence that hyperparathyroidism exists in renal rickets? In 1921 Pappenheimer and Minor[2] studied the parathyroids in 14 cases of human rickets and in 18 normal cases. They showed that there was a decided increase in the size of the parathyroids in the cases of rickets. This suggested possible hyperfunction. Hamilton and Schwartz[3,4] in 1932 and 1933 found that a large dose of calcium chloride or calcium gluconate given orally to rachitic rabbits caused a more marked rise in serum calcium than occurred in normal animals, and demonstrated that this property was transferable in rachitic blood. They showed this in the following way. Normal blood injected into rabbits after feeding them a large dose of calcium caused only a slight elevation as compared to that seen in the controls. However, when these animals were fed calcium and then injected with rachitic blood, a rise in blood calcium occurred which was much greater. The rise was identical to that seen after giving the animals parathyroid extract. They cautiously concluded that "the blood of rachitic rabbits is abnormally rich either in parathyroid hormone or in some other substance with identical effect on the serum calcium."

Shelling and Ramsen[5] applied this test to clinical cases of various types and found three positive tests. One was in a case of osteitis fibrosa cystica, one was in a case of florid rickets of several years' duration, and

one was in a case of renal rickets shown at autopsy to have reached hypertrophy of the parathyroid glands. The normal cases were calculated to contain from 3 to 7 units of parathyroid hormone per 100 cc. The case of osteitis fibrosa had 42 units per 100 cc., and the case of renal rickets had 14 units per 100 cc. In short, hyperparathyroidism according to this test was found in these three types of cases and might be considered primary in the first and secondary in the other two. This test was not applied in the case reported here.

SUMMARY

A case is presented of renal rickets in a 15 year old boy. The disease followed a deformity of the lower urinary tract and was associated with delayed puberty and enlargement of all the parathyroid glands.

The most important lesson to be learned from this case is that early effective treatment of the urinary obstruction probably would have prevented this fatal ailment.

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HEMATURIA; ITS CLINICAL SIGNIFICANCE

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Hematuria, although one of the more common symptoms of urinary disease, is frequently underestimated in its importance by the patient and often, unfortunately, by his physician. It should be emphasized that the presence of blood in the urine is not a clinical entity or disease per se, but rather a sign of an existing pathologic lesion requiring immediate and exhaustive investigation to determine the underlying etiologic factors.

Usually, the presence of gross blood in the urine is sufficiently alarming to cause the patient to seek medical advice. However, when the hematuria is intermittent, the cessation of the bleeding lulls the patient into a false sense of security; he may presume he is well. To the physician, however, this subsidence of hematuria is no indication that its significance is to be minimized. A complete urologic investigation should not be delayed.

Frequently, hematuria is the outstanding symptom. Often it is the only complaint, and at other times the blood may be only found upon microscopic examination. Fortunately, the bleeding in many instances is associated with concomitant symptoms. The presence of other symptoms often causes the individual to seek investigation and medical advice earlier than does the recognition of blood in the urine, although from the urologic point of view, the latter may be more serious. First among the symptoms is pain. Other complaints accompanying the hematuria may be burning and frequency of urination, chills and fever, sweats, the presence of a mass, loss of weight, history of trauma, etc.

MacKenzie[1] reported an excellent study of hematuria from the Royal Victoria Hospital in 1932. He stated that 20.24 per cent of urologic admissions passed urine containing blood, and in 75 per cent of the cases, the blood was caused either by tumor, infection, calculus, or nephritis. In 96 per cent of the cases with hematuria, a causative lesion was found within the urinary tract, and over 40 per cent of these lesions were neoplastic. Reports by Kretschmer,[2] Cahill,[3] the senior author,[4] and others have shown convincingly that blood in the urine is a serious symptom, and that its source and cause should be ascertained even though at times it may involve extensive examinations and lab-

oratory procedures. The type of bleeding may be of some aid in explaining its source; e.g., when it originates from the anterior urethra, the blood is usually initial and bright; terminal hematuria may arise from the posterior urethra or from the bladder; total hematuria is more often from the bladder, ureter, or kidney. However, these evidences are insufficient to ascertain the location of the pathologic lesion without complete urologic survey.

The following tabulation and grouping has been found very useful in classifying hematuria and emphasizes the most important causes of hematuria as seen at the Cleveland Clinic.

I. Hematuria in general disease

- A. Acute fevers: Tonsillitis, scarlet fever, rheumatic fever, etc.
- B. Chronic infections: Endocarditis (renal infarction), malaria
- C. Blood dyscrasias: Purpura, leukemia, hemophilia, polycythemia vera
- D. Deficiency and dietary disease: Scurvy and liver deficiency
- E. Diseases of unknown etiology: Hodgkin's disease, hypertension or arteriosclerosis with renal involvement, periarteritis nodosa
- F. Following medication: Sulfonamides, methanamine, salicylates, barbiturates, mandelic acid, etc.

II. Hematuria due to intrinsic diseases of the urinary tract

- A. Renal
  1. Calculi or crystals
  2. Nephritis
  3. Tumor—capsular, parenchymal, pelvic
  4. Infection—acute or chronic including tuberculosis
  5. Anomalies—polycystic disease, horseshoe kidney, nephroptosis, etc.
  6. Trauma
- B. Ureteral
  1. Calculi
  2. Infection
  3. Stricture
  4. Tumor
- C. Vesical
  1. Tumor
  2. Infection
  3. Calculi or foreign bodies
  4. Ulcer
  5. Trauma
- D. Bladder neck
  1. Prostate including seminal vesicles

E. Urethral
   1. Infection
   2. Stricture
   3. Tumor
   4. Following instrumentation

III. Hematuria associated with extraurinary pathology

A. Acute appendicitis
B. Diverticulitis of the colon
C. Neoplasm of the colon, rectum, or pelvic structures
D. Acute or chronic salpingitis

This classification is by no means exhaustive; practically every disease of the urinary tract at some time or other may be accompanied by hematuria. It does indicate, however, the extensive investigation which may be necessary to uncover the etiologic factor producing blood in the urine. Complete study of the urinary tract is essential: this includes cystoscopy, estimation of individual kidney function, examination of specimens of urine from each kidney, pyelography, and intravenous urography. With these procedures in addition to the routine physical examination and routine laboratory examination, an accurate diagnosis can be established in the vast majority of cases, and appropriate therapy instituted early in the course of the disease.

The following case reports illustrate a number of conditions associated with hematuria, and the investigation which may be necessary to disclose the cause of bleeding.

CASE REPORTS

Case 1. Hematuria due to blood dyscrasia. This patient was registered at the Clinic in 1933 at which time a diagnosis of rheumatoid arthritis was made. She returned in 1942 at the age of 23 with the chief complaint of marked weakness.

General physical examination was essentially negative except for pronounced pallor. The spleen was not palpable, nor was there lymphadenopathy.

Blood study showed a hemoglobin of 35 per cent; the red blood count was 1,780,000. Urinalysis showed many red blood corpuscles.

Further blood studies were undertaken. Fragility tests showed increased hemolysis. The smear revealed spherocytosis and autoagglutination of the red cells; the white blood count and differential study were normal; red cell volume was 40 per cent of normal; reticulocytes were 25.8 per cent; icterus index was 38; sternal puncture showed a hyperplastic marrow.

The final diagnosis was acquired hemolytic anemia. A splenectomy was done.

This patient showed microscopic hematuria, and urologic investigation was necessary to eliminate the possibility of a coexisting lesion in the urinary tract, although the laboratory tests readily disclosed the cause of the urinary tract hemorrhage.

Case 2. Hemorrhagic Bright's disease. A 22 year old woman first registered at the Clinic in 1940 at which time general examination revealed no abnormalities. Two years later, following an episode of sore throat which had been treated with sulfanilamide, she returned with the primary complaint of marked hematuria. Bloody urine had been present on every voiding for several weeks, but no blood clots had been passed. No other urinary symptoms were present.

Physical examination was essentially negative. Blood pressure was 106/80.

Blood count revealed a mild hypochromic anemia. The urine was grossly bloody. Urinalysis showed a specific gravity of 1.017, and a trace of albumin. Microscopic examination revealed many red blood cells, many casts, and an occasional white blood cell.

The blood urea was 39 mg. per cent; urea clearance was 73 per cent of normal the first hour and 74 per cent the second hour.

Although this appeared to be a "medical" renal disease, an excretory urogram and cystoscopy were done to eliminate a coexisting surgical disease of the urinary tract inasmuch as the bleeding had been profuse; both revealed normal findings.

The final diagnosis was mild hemorrhagic Bright's disease.

Case 3. Hematuria due to drug administration. A 44 year old man admitted to the Clinic Hospital with a chronic osteomyelitis of the right tibia was given a course of sulfathiazole therapy. He had received 27 Gm. of this drug and 7 Gm. of sulfadiazine when he suddenly developed pain in the right flank. The examination of the urine, which is made routinely during sulfonamide administration, revealed microscopic hematuria on repeated specimens. Because of this finding, urologic consultation was requested.

Cystoscopy showed a collection of acetylated sulfonamide crystals obstructing the right ureteral meatus. Ureteral catheterization and pelvic lavage were done. The sulfonamides were discontinued, and the patient was free both of renal colic and hematuria.

Diagnosis: Hematuria associated with the administration of sulfathiazole and sulfadiazine.

Case 4. Hematuria from a renal neoplasm. A 41 year old accountant registered at the Clinic with the complaint of passage of bright red blood and clots in the urine. There had also been a slight ache in the loin and loss of weight. The bloody urine had been present on every voiding for 3 days preceding examination, and several large clots had been passed.

Cystoscopy showed no bladder lesion. Retrograde pyelography disclosed a marked hydronephrosis of the right kidney. At operation, several neoplastic areas were present in the cortex of the kidney. Pathologic diagnosis revealed these to be sarcomatous nodules. Final diagnosis: Stromal sarcoma of the right kidney. The passage of blood clot would have led to the superficial diagnosis of bladder tumor, but complete investigation was necessary to disclose the true lesion.

Case 5. Hematuria resulting from the presence of a calculus. A 56 year old man came to the Clinic with the complaint of blood in the urine associated with pain in the left flank. The gross hematuria had been of intermittent character over an entire year, the pain becoming progressively more severe. The general physical examination revealed no abnormal findings. Urologic investigation disclosed the presence of a calculus in the left kidney. A left pelviolithotomy was performed, and the patient was relieved of

his symptoms. Final diagnosis: Calculus, left kidney. Here the hematuria had been minimized, and the patient had been brought under medical care only because of the pain.

Case 6. Hematuria due to coexisting pathologic lesions of the urinary tract. For the past 6 years a 32 year old man had been having episodes of recurring hematuria, particularly severe in the two months preceding the patient's registration at the Clinic. Grossly bloody urine had been present on many occasions during this period and had disappeared spontaneously. No clots had been passed. No other urinary symptoms had been present. An attack of left renal colic, which had occurred later and returned at intervals, finally caused him to seek medical aid.

The roentgenogram revealed a calculus in the left lower ureter. Manipulation of the calculus was decided upon, and at the time of cystoscopy a papilloma of the bladder was noted and fulgurized. This latter lesion apparently had produced the long-standing hematuria. Ordinarily, one might expect the passage of blood clots in the presence of a bladder tumor, but it can readily be seen that there is no characteristic pattern for hematuria with urologic lesions.

Final diagnosis: Left ureteral calculus and papilloma of the bladder.

Intermittent hematuria of several years' duration failed to bring this patient for medical advice. When pain appeared and the patient finally sought relief, complete urologic investigation revealed the presence of two coexisting pathologic conditions.

Case 7. Extensive bladder tumor as cause of hematuria. A 56 year old man registered at the Clinic in November 1942 with a complaint of recurring bloody urine since 1935. The hematuria would disappear spontaneously, only to return. Numerous blood clots had been passed. Since he had been troubled with no other symptoms, such as pain, he had disregarded the bloody urine until he had developed severe frequency and dysuria 7 years after the onset of the bleeding.

Except for pallor, the general physical examination was essentially negative. Blood count revealed a marked anemia. The urine was frankly bloody. Cystoscopy disclosed an extensive malignancy of the bladder. Bilateral hydronephrosis was demonstrated on intravenous urography.

Because of the extensive involvement of the bladder by the neoplasm, complete surgical resection could not be accomplished. X-ray therapy was administered. Diagnosis: Carcinoma of the bladder. The patient had ignored the recurrent bleeding from the bladder for 7 years until other symptoms prompted him to seek relief. A history of intermittent painless hematuria with passage of clots is characteristic of bladder tumor.

Case 8. Polycystic kidneys as a cause of hematuria. A 50 year old farmer reported that his urine had been bloody for 10 days prior to his visit to the Clinic in December 1941. The urine had ranged in color from "pink to red" on different voidings; no clots had been passed. No other urinary symptoms were present.

Physical examination revealed a large mass in the left upper quadrant, and a neoplasm of the left kidney was suspected. However, bilateral pyelograms disclosed the presence of typical congenital polycystic kidneys. Conservative treatment was advised.

Final diagnosis: Polycystic kidneys. Bleeding in these cases is not unusual, and accurate diagnosis must be made in order to avoid unnecessary exploratory surgery.

Case 9. Renal tuberculosis as cause of hematuria. A 28 year old man complained of pain in the left flank and associated gross hematuria with the passage of blood clots. The bleeding had been of only a week's duration and was present on each voiding, although clots were passed less frequently. No other urinary symptoms were present.

The patient was apparently in good health. No abnormalities were present on physical examination. By intravenous urography the right kidney was observed to be normal; the left kidney was insufficiently filled for diagnosis. Cystoscopy was then performed, and a pyelogram of the left kidney revealed a destructive lesion in the upper calyx suggestive of tuberculous infection. Later guinea pig inoculation was positive for tuberculosis.

Final diagnosis: Tuberculosis, left kidney. It is to be noted that although bleeding had been of but one week's duration, the kidney lesion was already well advanced. A nephrectomy was performed.

Case 10. Hematuria from prostatic varices and recurrent prostatic hypertrophy. A 73 year old man had a transurethral resection for hypertrophy of the prostate in 1935. He was symptom free for 7 years. He returned in 1942 with the history of bloody urine of 2 weeks' duration. Bleeding was present on each voiding, and numerous clots had been passed. There was no pain, nor other urinary symptoms. Bleeding had been rather profuse, and attempted cystoscopic visualization of the bladder was unsuccessful because of severe hemorrhage.

After the bleeding had been controlled by bladder irrigation, cystoscopy disclosed recurrent hypertrophy of the prostate with numerous dilated veins on the surface of the prostate. Rupture of these vessels accounted for the bleeding. A transurethral resection of the obstructing prostatic tissue was performed, and bleeding subsided.

Final diagnosis: Prostatic varices and recurrent prostatic hypertrophy.

From the previously reported cases, it is evident that from the history elicited from the patient and by a general examination the causative lesion responsible for the hematuria cannot be ascertained. Only by a comprehensive urologic survey aided by laboratory procedures can an accurate diagnosis be established and the proper therapeutic program instituted.

The clinical significance of hematuria cannot be minimized. Delay in establishing an accurate diagnosis frequently deprives the patient of the opportunity for a cure either by medical or surgical trestment, the therapy to be instituted depending upon the lesion present.

CONCLUSIONS

1. Hematuria is not a disease nor a clinical entity; it is merely a symptom which demands complete investigation and early diagnosis.

2. Although specific intrinsic diseases of the urinary tract usually account for hematuria, systemic disease may also be the cause of blood in the urine.

3. Complete medical and urologic study may be required to establish an accurate diagnosis. Early determination of the causative pathologic lesion is essential for a good prognosis.

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MULTIPLE MYELOMA WITH NITROGEN RETENTION

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The early clinical diagnosis of multiple myeloma is rendered difficult by the relative vagueness of the symptoms and by the scarcity of physical signs. The first symptoms are usually indefinite pains in the lower chest or the lumbosacral spine. Since the patient is usually in the fourth or later decades of life, these pains are apt to be regarded as being arthritic, myositic, or fibrositic in origin and are treated as such. Most patients, therefore, have increasing symptoms before a thorough investigation with careful urinalyses, blood studies, x-ray studies, serum protein determinations, and finally bone marrow studies establish the diagnosis. Albuminuria is a frequent finding, and renal failure is a common complication in well-defined cases.

In the following case an azotemia of unknown origin was the outstanding clinical feature without other indications of myeloma. The original problem was to explain an increased blood urea, and the correct diagnosis was only determined by methodical elimination of the various causes of azotemia. In retrospect, however, the history was more suggestive of the diagnosis than it appeared to be at first consideration.

CASE REPORT

A Greek restaurateur, age 42, was admitted to the Clinic August 6, 1942, with the chief complaint of nausea and vomiting of 3 weeks' duration. He stated that he had been well until the preceding June, at which time following heavy lifting he had experienced a very severe pain in the left costal margin and left lower chest. It had persisted for several days and had been associated with cough and sputum. It had been partially relieved by the application of adhesive plaster, but some localized tenderness had remained over the affected area. Hematuria had not been present at the time of injury, but 3 weeks subsequently the patient had developed diurnal urinary frequency without dysuria occurring every 2 to 3 hours and nocturnal frequency two or three times. Three weeks before admission he had begun to vomit approximately an hour after meals, and at the time of admission he was unable to retain any food. There had been no epigastric pain at any time, and hematemesis was denied as well as melena. He had lost 25 pounds in weight since the onset of the illness which had been completely afebrile as far as he was aware. Albumin had been found in the urine, and the patient had been treated for kidney disease. Further history appeared irrelevant.

Physical examination revealed a well-developed and adequately nourished, rather healthy looking adult. The skin and mucous membranes were normal in color and tex-

ture. The pulse rate was 92, the temperature 97 F., the blood pressure 110/70. The pupils were equal and reacted normally to light and accommodation. The optic disks were clearly outlined, and the retinae appeared normal. The ear drums were clean and shiny. The maxillary sinuses were somewhat dull to transillumination. There was considerable dental repair with several gold crowns and well-marked pyorrhea and gingivitis. There were no palpable lymph nodes in the neck and no thyroid enlargement. The chest was symmetrical, and the respiratory movements were normal. Slight tenderness was demonstrated in the left chest anteriorly, but no swelling was noted over any of the ribs. The heart was of moderate size, regular, and rhythmic. There was no palpable enlargement of the kidneys, liver, or spleen, and no abdominal masses. Some tenderness was elicited on deep pressure over both costovertebral angles. The external genitalia were of normal male type. A bilateral inguinal hernia was present. The rectal sphincter was of normal tone, and the prostate of normal size and consistency. Neurologic examination revealed hyperactive reflexes, but no abnormal reflexes were elicited, and there were no sensory nor motor changes. No gross skeletal abnormalities were demonstrated.

A routine urinalysis was reported as follows: pH 4.5, specific gravity 1.015, albumin 3 plus, sugar negative; microscopically, numerous white blood cells were seen. There were 3,500,000 red blood cells, with a hemoglobin of 68 per cent; and 9,650 white blood cells. The fasting blood sugar was reported as 116 mg. per cent. The blood Wassermann and Kahn reactions were negative. The urea clearance test of the renal reserve showed 52 per cent function in the first hour, and 44 per cent in the second hour. Blood urea was 156 mg. per cent.

An x-ray of the chest was reported as being normal. Films of the lumbosacral region were reported normal with the exception of a little osteo-arthritis. There were no suspicious urinary tract shadows, and both kidneys were normal in size and position. There were, however, many calcifications in the prostate. An excretory urogram showed poor function in both kidneys. The total renal function was not of sufficient quantity during the one-hour period for diagnosis. A cholecystogram revealed a normally functioning gallbladder without evidence of calculi. The esophagus, stomach, and duodenum appeared normal except for some hypertrophy of the gastric rugae. During fluoroscopy there was no obstruction to the passage of barium. The colon showed no evidence of organic lesion. There was no evidence of diaphragmatic hernia. The absence of free hydrochloric acid was demonstrated in the gastric juice even after histamine stimulation on two occasions, with a total acidity of 25 on the first test and 60 on the second.

The patient was given intravenous glucose using a maximum of 2,000 cc. of 10 per cent glucose in normal saline daily. Considerable clinical improvement was manifested within a few days, and at the end of a week the patient was able to retain a normal diet but still complained of generalized pain of rather indefinite character. At the end of 2 weeks the blood urea was 39 mg. per cent having steadily decreased from the initial elevated reading. In the meantime routine urinalysis had shown only a small amount of albumin and a few white blood cells. A culture of urine was reported as showing a Staphylococcus albus of nonurea-splitting type. Retrograde pyelography and cystoscopy were carried out with entirely negative results.

Further investigation revealed the true nature of the underlying condition. A test for Bence-Jones protein in the urine was positive. A recheck of the blood count showed 2,610,000 red blood cells, with a hemoglobin of 49 per cent; and 4,100 white blood cells. The volume of packed cells was 51 per cent of normal, the volume index 0.98, color index 0.94, and saturation index 0.96. Erythrocytes showed slight anisocytosis and slight pallor, but were normal in shape on stained preparation. No regenerative forms were

seen. The differential leukocyte count showed 61 per cent neutrophiles, 30 per cent lymphocytes, 1 per cent eosinophiles, and 8 per cent monocytes. No abnormal forms were seen. The icteric index was 4, and the platelets were normal. Marked rouleaux formation was noted. The serum proteins totaled 9 mg. per cent, of which albumin constituted 4 mg. per cent and globulin 5 mg. per cent.

Sternal puncture was easily performed, the sternal cortex being soft and thin. Approximately ½ cc. of bloody material was obtained, and on stained preparation numerous atypical plasma cells were the only recognizable cellular elements.

Subsequently, an x-ray of the skull revealed numerous extensive defects suggestive

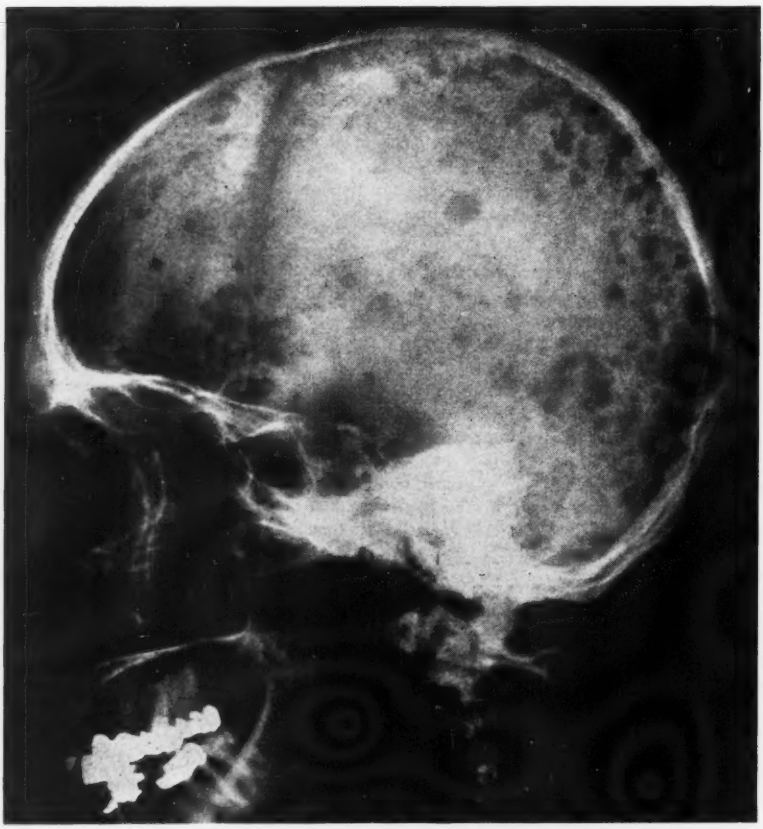

Figure 1

X-ray of the skull showing characteristic bony defects of multiple myeloma.

of multiple myeloma, and a more critical examination of the chest x-rays revealed several areas in the ribs at least suggestive of myelomatous degeneration which had been previously overlooked.

DISCUSSION

This patient presented many characteristic signs of multiple myeloma. The case illustrates the necessity for considering this condition in the differential diagnosis of vague generalized pain. He reported an episode of acute pain in the lower chest which has been noted in many of our cases. Physical examination was of little aid in establishing the diagnosis, although once it had been made, very definite localized tender areas could be demonstrated on several of the ribs. No definite thickening could be discerned, and no egg-shell crackling of the cortex was elicited. The presence of Bence-Jones proteinuria was readily established. Renal failure occurred earlier than usual, and uremia dominated the clinical picture when the patient was first seen. The anemia was not so marked as frequently occurs. A moderate lymphocytosis was present, but no eosinophilia and no atypical plasma nor myeloma cells were seen in the smear. Immaturity of the red or white blood cells could not be demonstrated. The rouleaux formation, which has been described as being characteristic of this condition, was very evident. The total serum protein was considerably elevated with characteristic reversal of the albumin-globulin ratio. X-ray studies of the chest and spine failed to reveal the characteristic changes on first observation. In studies of the skull, however, the characteristic changes were immediately obvious despite the fact that the patient had no local symptoms. The great value of studies of the bone marrow by sternal puncture is evident.

No specific therapy for this relatively rare disease is available. X-ray irradiation over localized painful areas is of some symptomatic value. The etiology is still obscure. Generally, it has been regarded as a neoplasm originating from some cell of the bone marrow. By other writers it has been related to an atypical leukemia, and because of this conception the term myelomatosis has been used.

TO FORMER FELLOWS OF THE CLEVELAND CLINIC FOUNDATION

For the past year we have been attempting to keep an accurate record of the ranks, services, and stations of all former Fellows who are on active duty with the Armed Forces of the United Nations. In the near future we plan to send a list of these names and addresses to all former Fellows. It is urgently requested that each Fellow send to Dr. A. T. Bunts his changes in rank and station as soon as possible as well as any information he may have regarding other Fellows.